An IL-17A crystallization system supporting small molecule structure-based drug design

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Interleukin 17A (IL-17A) is produced by activated T-cells and belongs to a family of proinflammatory cytokines responsible for host and innate immune responses. The inflammatory responses are triggered by IL-17A interacting with its membrane bound cell surface receptor (IL-17R). Dysregulation of IL-17A can lead to several autoimmune disorders such as rheumatoid arthritis, psoriasis and inflammatory bowel disease. Disrupting the IL-17A – IL-17R interaction is a way to reduce inflammation and treat autoimmune diseases, and several monoclonal antibodies targeting IL-17A – IL-17R are currently clinically approved. Limitations imposed by mAbs such as non-oral administration, long half-life, poor tissue penetration, are the reasons why several drug development companies are interested in small molecule inhibitors of IL-17A. In a recent publication (Andrews et al. 2022, Journal of Medicinal Chemistry), the development of a clinical candidate is described. The publication provides insight into how small molecule inhibitors can effectively modulate IL-17A activity. The X-ray co-crystal structures of two small molecule inhibitors of IL-17A presented in the article were determined by SARomics Biostructures. This unique crystallization system allows for co-crystallization with various small molecules without the need for stabilizing Fab molecules. The crystal structure resolution is ligand dependent and varies between 2-3 Å. This system is therefore useful for providing structural information to structure-based drug design campaigns. In addition, IL-17A apo crystals have successfully been obtained, which enables crystallographic fragment-based screening.